Reply to

Reply to: MSC-derived Exosomes: Are They Another Therapeutic Method for ECMO-supported ARDS?

Jonathan E Millar, MD[1,2], Jacky Y Suen, PhD[2], Daniel F McAuley, MD[3], John F Fraser, MD, PhD[2], on behalf of all authors of 'Combined Mesenchymal Stromal Cell Therapy and Extracorporeal Membrane Oxygenation in Acute Respiratory Distress Syndrome: A Controlled Experimental Study in Sheep.'

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To the Editors,

We thank Zhang and Hei for their insightful comments on our study of mesenchymal stromal cells (MSCs) in a sheep model of extracorporeal membrane oxygenation (ECMO) and Acute Respiratory Distress Syndrome (ARDS) (1). Their principal thesis is that the adverse interaction which we observed, between MSCs and the membrane oxygenator, may be overcome by substituting MSCs with MSC-derived exosomes. This proposal has merit. The MSC secretome has been of interest as a therapeutic for some time, in particular; MSC-derived extracellular vesicles (EVs) (2), MSC-derived exosomes (3), and MSC conditioned media (4). These each offer several theoretical advantages over conventional MSC therapy. First, contents of the secretome do not express Major Histocompatibility Complex (MHC) antigens, removing concerns about immunogenicity. Second, components of the secretome are, in general, easier to store and less susceptible to the adverse effects of storage on efficacy. Third, components of the MSC secretome are much smaller than the cells from which they are derived, and thus less likely to be subject to 'trapping' in the pulmonary circulation (5). Recently, an early phase trial of an MSC-derived exosome treatment for severe COVID-19 has been reported with no apparent safety issues (6). However, there are some unresolved issues which should be borne in mind.

Paracrine actions are the principle means by which MSCs exert benefit in ARDS, although several alternative mechanisms have been described, such as mitochondrial transfer from MSCs to damaged alveolar epithelial cells (7). The inability of secretome-based therapies to reproduce these actions may limit their efficacy (8,9). The translation of MSC secretome-based therapies is also limited by challenges in scaling manufacturing for clinical purposes, an issue which is overcome by the use of induced pluripotent cell-derived MSCs (iPSC MSCs),

like those used in our study (1). With specific regard to our study, the observation that pulmonary emboli were more frequent in the iPSC-derived MSC group, may not be uniquely associated with the use of a cell-based therapy. A variety of pre-clinical studies have described the pro-coagulant activity of MSC-derived EVs (10, 11).

Despite these caveats, Zhang and Hei's point is well made and highlights the work that is still required to successfully advance cell-therapy for ARDS, especially in the context of extracorporeal organ support. We hope that our study illustrates the usefulness of clinically relevant, high-fidelity animal models in advancing these efforts.

References

(1) Millar JE, Bartnikowski N, Passmore MR, Obonyo NG, Malfertheiner MV, von Bahr V, et al. Combined Mesenchymal Stromal Cell Therapy and Extracorporeal Membrane Oxygenation in Acute Respiratory Distress Syndrome. A Randomized Controlled Trial in Sheep. *Am J Respir Crit Care Med* 2020;2020(3):383-392.

(2) Abraham A, Krasnodembskaya A. Mesenchymal stem cell-derived extracellular vesicles for the treatment of acute respiratory distress syndrome. Stem Cells Transl Med 2020; 9(1): 28-38.

(3) Xu B, Chen SS, Liu MZ, Gan CX, Li JQ, Guo GH. Stem cell derived exosomes-based therapy for acute lung injury and acute respiratory distress syndrome: A novel therapeutic strategy. Life Sci 2020; 254: 117766.

(4) Emukah C, Dittmar E, Naqvi R, Martinez J, Corral A, Moreira A, Moreira A. Mesenchymal stromal cell conditioned media for lung disease: a systematic review and meta-analysis of pre-clinical studies. Respir Res 2019; 20(1): 239.

(5) Kraitchman DL, Tatsumi M, Gilson WD, Ishimori T, Kedziorek D, Wlaczak P, Segers WP, Chen HH, Fritzges D, Izbudak I, Young RG, Marcelino M, Pittenger MF, Solaiyappan M, Boston RC, Tsui BMW, Wahl RL, Bulte JWM. Dynamic imaging of allogenic mesenchymal stem cells trafficking to myocardial infarction. Circulation 2005; 112(10): 1451-1461.

(6) Sengupta V, Sengupta S, Lazo A, Woods P, Nolan A, Bremer N. Exosomes derived from bone marrow mesenchymal stem cells as a treatment for severe COVID-19. Stem Cells Dev 2020; 29(12): 747-754.

(7) Islam MN, Das SR, Emin MT, Wei M, Sun L, Westphalen K, Rowlands DJ, Quadri SK, Bhattacharya S, Bhattacharya J. Mitochondrial transfer from bone-marrow-derived stomal cells to pulmonary alveoli protects against acute lung injury. Nat Med 2012; 18(5): 759-65.

(8) Hayes M, Curley GF, Masterson C, Devaney J, O'Toole D, Laffey JG. Mesenchymal stromal cells are more effective than the MSC secretome in diminishing injury and enhancing recovery following ventilator-induced lung injury. Intensive Care Med Exp 2015; 3: 29.

(9) Silva JD, de Castro LL, Bragga CL, Oliveira GP, Trivelin AS, Barbosa-Junior CM, Morales MM, dos Santos CC, Weiss DJ, Lopes-Pacheco M, Cruz FF, Rocco PR. Mesenchymal stromal cells are more effective than their extracellular vesicles at reducing lung injury regardless of acute respiratory distress syndrome aetiology. Stem Cells int 2019. doi: 10.1155/2019/8262849. Online ahead of print.

(10) Silachev DN, Goryunov KV, Shpilyuk MA, Beznoschenko OS, Morozova NY, Kraevaya EE, Popkov VA, Pevzner IB, Zorova LD, Evtushenko EA, Starodubtseva NL, Kononikhin AS, Bugrova AE, Evtushenko EG, Plotnikov EY, Zorov DB, Sukhikh GT. Effect of MSCs and MSC-derived extracellular vesicles on human blood coagulation. Cells 2019; 8(3): 258.

(11) Fiedler T, Rabe M, Mundkowski RG, Oehmcke-Hecht S, Peters K. Adipose-derived mesenchymal stem cells release microvesicles with procoagulant activity. Int J Biochem Cell Biol 2018; 100: 49-53.